II. REMARKS

Upon entry of the present amendment, claims 1, 7 to 9 and 12 to 33 will be pending. For the Examiner's convenience, a marked up copy showing the amendments to the claims is attached hereto as Exhibit A.

A. Regarding the Amendments and New Claims

Claims 2 to 6, 10 and 11 are canceled herein without disclaimer, and without prejudice to Applicant pursuing prosecution of subject matter encompassed within one or more of the claims in an application claiming the benefit of priority of the subject application.

Claim 1 has been amended to indicate that the method is directed to treating a "malignant cell proliferative disease" associated with "decreased expression of a 5'ALT polynucleotide" or with "expression of a mutant 5'ALT polypeptide." Claim 1 also has been amended to require contact of the cells to be treated with a "polynucleotide encoding" a 5'ALT polypeptide, and to clarify that "expression of said polynucleotide...suppresses proliferation" of the cells. The amendments are supported, for example, by previously pending claims 3 and 5, and in the paragraph bridging pages 29 to 30.

Claims 7 and 8, which depend from claim 1, have been amended to correspond to amended claim 1. As such, the amendments to claims 7 and 8 address formalities, and are supported as for the amendments to claim 1.

Claim 9 has been amended similarly to claim 1, in that the cell is defined as a "malignant" cell and the "reagent" is a "polynucleotide encoding a 5'ALT polypeptide." As such, the amendments to claim 9 are supported as for the amendments to claim 1.

New claims 12 to 33 have been added. New dependent claims 12, 22, 23, 30 and 31 are supported, for example, by claim 8, and in the paragraph bridging pages 35 to 36. New dependent claims 13, 14, 24, 25, 32 and 33 are supported, for example, in the paragraph bridging pages 36 to 37. New dependent claims 15 to 17, 19 to 21, and 27 to 29 are supported, for example, at page 5, lines 10-19, and at page 35, first paragraph.

New independent claim 18, directed to a method of treating malignant cells characterized by decreased expression of 5'ALT, and new independent claim 26, directed to a method of treating malignant cells characterized by expression of a mutant 5'ALT polypeptide, are supported, for example, by the paragraph bridging pages 29 to 30.

B. Rejections under 35 U.S.C. § 112

The rejection of the claims under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite respectfully, as set forth in the final Office Action (Paper No. 8) and maintained in the Advisory Action (Paper No. 11), respectfully is traversed.

It was stated in the final Office Action that the claimed methods, directed to a method of treating a disorder "associated with expression" of either 5'ALT or p16 expression with a "reagent" is unclear because the identify to the reagent is unclear and because the claims do not recite a specific disease. Although Applicant traverses the rejections for the reasons set forth in the response to the final Office Action, the claims nevertheless have been amended to indicate that the "disorder" is a "malignant cell proliferative disorder" (i.e., a cancer) that is characterized by "decreased expression of a 5'ALT polynucleotide" or by "expression of a mutant 5'ALT polypeptide" in order to advance prosecution of the subject application; and that the "reagent" is a "polynucleotide encoding a 5'ALT polypeptide". As such, it is submitted that claims as

such that one skilled in the art would know the metes and bounds of the claimed invention. Accordingly, it is respectfully submitted that the previous rejection of the claims under 35 U.S.C. § 112, second paragraph, is moot with respect to the present claims.

The objection to the specification and corresponding rejection of claims 1 to 11 under 35 U.S.C. § 112, first paragraph, as allegedly containing lacking enablement, as set forth in the final Office Action (Paper No. 8) and maintained in the Advisory Action (Paper No. 11), respectfully are traversed.

It was maintained in the final Office Action that the specification does not disclose how one readily identifies a cell proliferative disorder associated with 5'ALT and with p-16, or how to predictably treat such disorders using gene therapy. As to the identification of cell proliferative disorders amenable to treatment according to the invention, it is submitted that, in view of the amendments as discussed above with respect to the rejection under 35 U.S.C. § 112, second paragraph, and further in view of the specification, one skilled in the art would have known how to readily identify malignant cell proliferative disorders. In this respect, Applicants point out that methods of identifying "malignant cell proliferative disorders" (i.e., cancers) are well known in the art, and that the specification discloses that such disorders, which are characterized by decreased expression of 5'ALT polynucleotide or expression of mutant 5'ALT polypeptide, readily can be identified using routine methods such as northern blot analysis (see page 32, lines 10-17) or Southern blot analysis, which can detect allelic loss or methylation of the genomic region encoding a 5'ALT polypeptide (see Examples 6 and 7, pages 59-63). In addition, the specification provides specific examples of malignant cells encompassed within the claims, including, for example, small cell and non-small cell lung carcinoma cells, head and neck squamous cell carcinoma cells, and malignant glioma cells, each of which includes cells that are

which is a 5'ALT polypeptides (see Example 10, page 65-67; see, also, Examples 6-8, pages 59-63). As such, it is submitted that one skilled in the art would have known malignant cell proliferative disorders that can be treated according to a method of the invention, and further would have known how to identify other malignant cell proliferative disorders amenable to such treatment without undue experimentation.

As to practicing methods of gene therapy, Applicants pointed out in response to the first Office Action (Paper No. 3) that the Stolberg article, which is a NY Times article that was cited by the Examiner in support of the position that gene therapy is unpredictable, provides several examples demonstrating the effectiveness of methods of gene therapy. Specifically, Applicants pointed out that Stolberg states that clinical trials of gene-based treatments for hemophilia are showing promise, and certain cancer patients appear to respond to gene therapy (page 1). For example, the Stolberg article describes three hemophilia patients that have received a dose of gene therapy of Factor IX, which was so low that it was not effective in dogs, showed expression of Factor IX such that their conditions improved and their need for standard treatment was reduced (page 4). In addition, the article describes four of five babies that were born with SCID and treated by gene therapy had normal immune responses 10 months after receiving gene therapy (paragraph bridging pages 4-5). The article further describes a child with adenosine deaminase deficiency that was successfully treated using gene therapy (page 5, second full paragraph). In addition, the article describes results of a trial by Vical showing that gene therapy of advanced skin cancer patients resulted in positive results in 25% of the treated patients, a result that is remarkable due to the advanced stage of the disease and the fact that the patients had failed all other treatments (page 5, last three paragraphs).

In the [illegible] Office Action it was argued that all of the positive results specific treatments

associated with the absence of a gene product. In the Advisory Action, it was stated that the specification provides no description or working examples of a method of gene therapy to treat any cell proliferative disease, and provides no working example of any reagent that modulates expression of 5'ALT to treat a cell proliferative disorder (emphasis in Advisory Action, page paragraph 1), and that the Stolberg reference does not overcome these "deficiencies" nor does the reference provide guidance to enable the full scope of the claims.

Applicants point out, however, that the specification does provide a description of a method of gene therapy to treat cell proliferative disorders characterized by abnormal expression of a 5'ALT polypeptide, and further provides a description of a reagent for practicing the method, i.e., a polynucleotide in a vector or formulated in colloidal dispersion system (see, for example, pages 29-35). Notwithstanding the broad disclosure in the specification, Applicants point out that the claims as amended (and the new claims) are not directed to treating "any" cell proliferative disorder with "any" reagent, but are more specifically directed to methods of treating a "malignant cell proliferative disorder" having the recited characteristics with a "polynucleotide encoding a 5'ALT polypeptide." As such, it is submitted that, in view of the Stolberg reference, which discloses that gene therapy can be effective for treating specific disorders associated with aberrant expression of specific genes, one skilled in the art, viewing the specification, would have known that a method of gene therapy as claimed reasonably would have been expected to be useful for treating a malignant cell proliferative disorder having the recited characteristics.

As further evidence that the specification would have enabled one skilled in the art to practice a method of the invention as claimed, Applicants submitted with the response to the final Office Action the Liggett et al. reference (Cancer Res. 56:4119-4123, 1996), which was published after the June 30, 1995, priority date of the subject application. However, as indicated

Office Action was mailed, elected not to consider the reference. Accordingly, Applicants have resubmitted the Liggett et al. reference herewith (Exhibit B), and respectfully request that the Examiner consider the reference.

Liggett et al. describe, for example, that introduction of a polynucleotide encoding p16β (i.e., 5'ALT-p16) into cells of a head and neck squamous cell carcinoma (HNSCC) cell line or into HeLa cells resulted in growth inhibition of the tumor cells (see Exhibit B; Abstract). Significantly, the various HNSCC malignant cells are associated with expression of a mutant 5'ALT polypeptide (truncated) or with hypermethylation of the p16 promoter region (Exhibit B, Table 1, page 4120; see, similarly, Examples 6-10 of the specification, pages 59-67, disclosing methylation of p16 in HNSCC). Thus, the Liggett et al. reference demonstrates that introduction of a polynucleotide encoding a 5'ALT polypeptide (i.e., 16β/5'ALT-p16) into HNSCC cells can inhibit the growth of the malignant cells and, therefore, provides confirmatory evidence that, as disclosed in the specification, a polynucleotide encoding a 5' ALT polypeptide can treat a malignant cell proliferative disorder.

It is noted that the Liggett et al. reference is being submitted only to confirm that the specification as filed would have enabled one skilled in the art to practice the claimed methods (see Gould v. Quigg, 3 U.S.P.Q.2d 1302 (Fed. Cir. 1987); later dated publication can be used as evidence that the disclosed invention was operative, Id. at page 1305). It is maintained that the specification enables the claimed invention for the reasons set forth above and in responses to the previous Office Actions.

In summary, it is submitted that one skilled in the art, viewing the specification, would have known that a malignant cell proliferative disorder associated with decreased expression of a

method of the invention, would have known specific examples of such malignant cell proliferative disorder and routine methods for identifying additional such disorders, and would have known that a method of a gene therapy using a polynucleotide encoding a 5'ALT polypeptide can be used to effectively treat such as disorder. The Liggett et al. reference submitted herewith provides confirmatory evidence that such a method can effectively treat a malignant cell proliferative disorder, as disclosed in the specification. Accordingly, it is respectfully requested that the objection to the specification be withdrawn and that the corresponding rejection of the claims under 35 U.S.C. § 112, first paragraph, be removed.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: January 10, 2002

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EXHIBIT A

MARKED UP COPY OF CLAIMS SHOWING THE AMENDMENTS

1. (Twice amended) A method of treating a malignant cell proliferative disorder associated with decreased expression of a 5'ALT polynucleotide or expression of a mutant 5' ALT polypeptide, the method comprising contacting [the cell] cells having or suspected of having the disorder with a [reagent which modulates expression of the] polynucleotide encoding a 5'ALT [polynucleotide or activity of a] polypeptide [encoded by said polynucleotide], whereby expression of said polynucleotide encoding a 5'ALT polypeptide suppresses proliferation of the cells, thereby treating the malignant cell proliferative disorder.

7. (Amended) The method of claim 1, wherein the malignant cell is derived from lung, pancreas, blood, head or neck.

7. (Amended) The method of claim 1, wherein the malignant cell is derived from lung, pancreas, blood, head or neck.

8. (Twice amended) The method of claim 1, wherein the [reagent] polynucleotide is introduced into the malignant cell using a vector.

9. (Twice amended) A method of treating a subject having a malignant cell proliferative disorder associated with altered p16 expression due to methylation of a CpG island of a p16 gene in a cell, the method comprising administering to a subject with the disorder, a therapeutically effective amount of [reagent which modulates expression of the p16 gene] a polynucleotide encoding a 5'ALT polypeptide, whereby expression of the polynucleotide in malignant cells in the subject suppresses proliferation of the malignant cells, thereby treating the subject.